Pharmacia & Upjohn

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 99D-0529; Draft Guidance for Industry on Changes to an Approved NDA or ANDA; Notice of Availability and Request for Comments; Federal Register, Monday, June 28, 1999 (64FR34660)

Dear Sir/Madam:
We are pleased to submit comments on the referenced draft guidance. We have the following general comments about the draft:

- While there is good evidence of sound scientific principles in many sections of the guidance, overall it suffers from attempting to be too comprehensive as opposed to the very topically oriented SUPAC series.

- The concept that some previously issued guidances may be partially superceded by this guidance can be logically understood but creates practical difficulties to both industry and FDA reviewers. We support future FDA efforts to either update or delete guidances that are superceded. If this guidance were issued as is, it would be a departure from the clarity achieved in other recent CMC communications.

- In the introduction to the guidance it should be clearly stated that the specific requirements defined by this guidance are only applicable to approved registrations containing such information. They should not be retrospectively applied. For example, if an extant registration provides no description of buildings, rooms, or equipment, such changes within sites approved for manufacture of a drug substance or drug product need not be reported to FDA.

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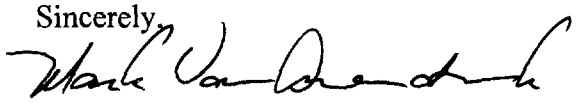
- We find a number of statements in this guidance that are more correctly the subject of GMP regulations and suggest that they be deleted. These are enumerated below in the line-by-line comments.

Our other specific comments are attached for various items in the draft.

Sincerely,



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Line 89:
Cover letters are not required for the annual reports for NDAs or ANDAs, therefore this does not apply. Rewrite sentence as "in the cover letter of the supplement or summary pages of individual sections of the annual report."

Lines 105, 107, 111:

Replace "validate, validates, validating" with the appropriate form of the word "assess". This is what is intended. Also, delete footnote #5; it will no longer be needed.

Lines136-138:

Delete the sentence beginning "This additional assessment...by the change." It is redundant and confusing relative to the subsequent discussion.

Lines 197-198:

Delete the term "establishments". The impression is given that the terms "sites", "facilities" and "establishments" are interchangeable or have the same meaning. "Sites" and "facilities" are equivalent terms, but establishment may be considered to mean the legal corporate entity rather than a specific geographical location.

Lines 213-216

What defines a discontinued operation? We propose to include the following definition in the glossary: "A discontinued operation is one where the registration holder has deleted the site for this operation from the NDA or ANDA and that is no longer subject to an establishment fee." Without clarification and definition of this term, the NDA or ANDA holder is potentially required to inform FDA to restart manufacturing operations that are campaigned with one another or operations that are run infrequently do to the market demand for the drug substance or drug product.

Lines 216-221:

This should be moved to the Manufacturing Process section; it describes process changes rather than general issues.

Line 227:

Start a new paragraph starting with, "For sites used to " for ease of reading.

Lines 250-252:

The definition of "discontinued" operations needs to be understood by presenting it in the glossary. Please see comment on lines 213-216.

Lines 258-260:

These should be deleted. Process changes and site changes are often independent of one another and a process change does not necessarily imply a move to a new site. The assessment of cross contamination issues is automatically done as a QA function to meet existing GMP regulations.

A better example of an operation that would be materially different after a change is one in which process filtration has been changed from Nutsche to ultrafiltration technology.

Line 289:

The example of room changes should be qualified that it cannot be a new room or refurbished room.

Line 290:

Insert the word "sterile" before the words "drug product".

Lines 303 and 305:

The words "the same" should be deleted; a change within the same campus, should not be a site change.

Lines 311-313:

Modify this to read "The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product, and may be considered if the approved application is impacted by such changes." This is to say that the types of changes listed here only need to be reported if the approved application lists specific sites, rooms, buildings, or floor plans associated with an activity.

Lines 317-322:

Items 3 and 4 in should be deleted; site changes within a campus need not be reported except for sterile drug substances or drug products. Typically registrations for non-sterile drug substances and drug products do not include this level of detail.

Lines 333-336:

These lines should also be deleted. Item #7 is covered under manufacturing process changes and item #8 is of no impact and is vague and undefined in scope or content.

Line 382:

Deletion of equipment does not necessarily infer that the change will have an adverse effect on identity, strength, quality, purity or potency of the product. Consider allowing equipment deletion to be submitted as special supplement - changes being effected, 30-day implementation.

Lines 402-407:

The definition of "natural product" is unclear. Since this draft guidance does not cover specified biotechnology and specified synthetic biological products, this section appears to address traditional fermentation and bioconversion technologies. The second bullet point should be more precise. Consider for example, "Changes in the source material (e.g. genus and/or species of microorganism or plant) or cell line. The third bullet point should also be modified; for example consider "Establishment of a new master cell bank or seed for a different genus and/or species of microorganism or cell line.

Line 413:

The example is weak. In drug substance manufacturing, filtration to collect a product is often performed using a basket centrifuge. Hence, there is some blurring of terminology. A better example is a change from Nutsche filtration to ultrafiltration.

Line 414:

Delete this line; it is redundant to the items in lines 415-420.

Lines 418-420:

Change the wording to "...that adversely affects its impurity profile or changes the physical, chemical, or biological properties...".

Lines 421-423:

Delete the word "code" in line 421 and add to the end of line 423 "or identified on the GRAS listing".

Line 492:

Some drug substance manufacturers purchase bulk raw materials of a single quality that are used in several processes as well as in steps before or after the final intermediate. Such materials have single sets of tests and are tested against single sets of specifications regardless of where they are used in the process. This circumstance combined with requirements in the guidance for a higher level of FDA review for changes associated with materials used to produce the final intermediate and API will negatively impact

some API manufacturers' abilities to implement changes to the specifications and test methods for starting and raw materials. Preferably, the same requirements identified in this guidance and in BACPAC I for changes to specifications and test methods for raw and starting materials used in the early steps of the synthesis would also apply to these materials used in the preparation of the final intermediate and drug substance.

Lines 501-504:

General limits for monitoring the production environment are a GMP requirement and should not be the subject of control through an approved application.

Lines 540-543:

This should be an annual report or at the most an immediate Changes Being Effected.

Line 559:

After "drug", add "substance or drug product".

Line 567

Replace 567-571 with "Any change made to comply with the addition, change or deletion of an official compendial method." The currently suggested language in this section is of limited value because it results in the potential for multiple sets of tests to comply with FDA and USP requirements.

Line 584-5:

The maintenance of reference standards is a GMP requirement and should not be required to be reported.

Lines 599, 602, 616 and 619:

Delete the word "particular". As used, the word "particular" implies a special meaning that is not defined.

Lines 628-633:

Keep the flow of each bullet point consistent, i.e. "from...to..." or vice versa.

Lines 638-639:

Delete "sterile drug substance".

Line 650:

Add an item. Consider the wording "A change of tablet count in a registered container closure system when not bracketed by stability data. (A stability commitment must be included.)"

Lines 661-662:

Add after "units" the following: "or a change in the tablet count when it is bracketed by existing stability data".

Line 663:

Add a bullet point to this section: "Addition of a desiccant".

Line 790-2

Replace "full production batches" with "full production batches or batches that would meet the definition of primary stability batches as found in the ICH Guidance on Stability, Q1A."

Lines 794-799:

Delete this section. It is not a current requirement and is more properly controlled by existing GMP regulations.